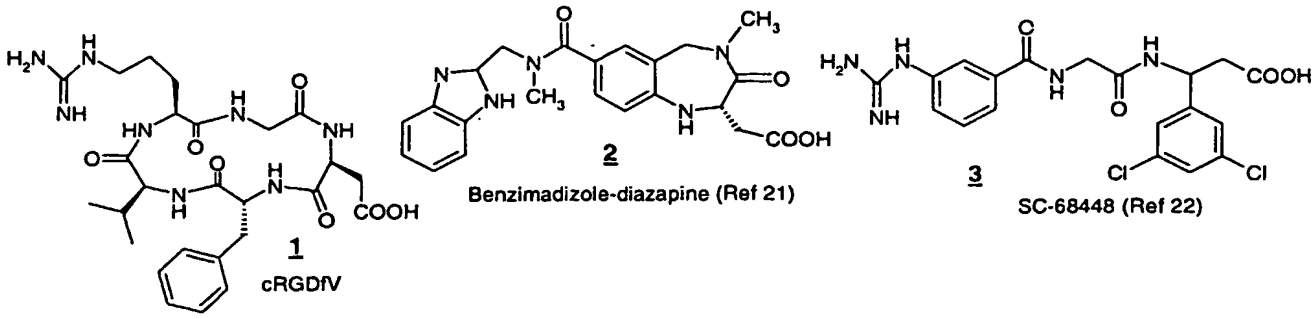

1
cRGDfV
cyclo-(-Arg-Gly-Asp-D-Phe-Val-)
2
Benzimadizole-diazapine (Ref 21)
3
SC-68448 (Ref 22)

Fig. 1

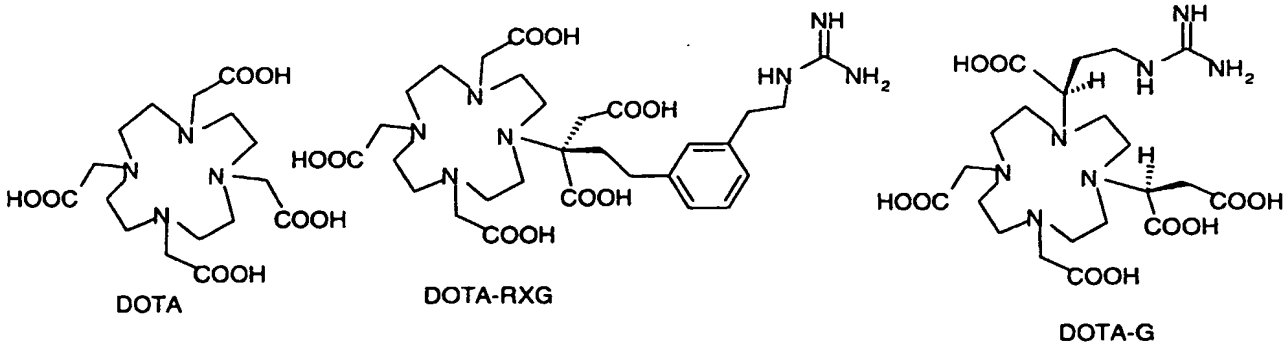
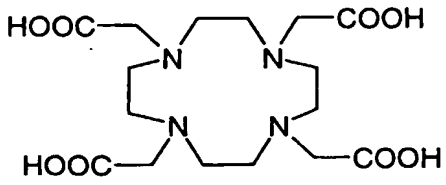
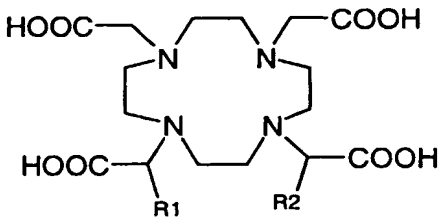

DOTA
DOTA-RXG
DOTA-G

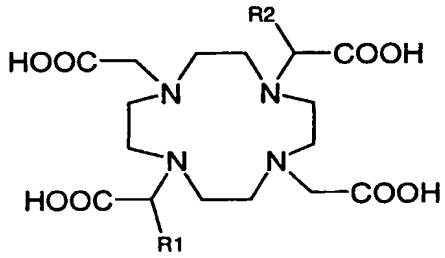
Fig. 2



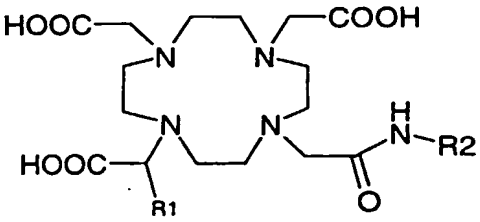
DOTA



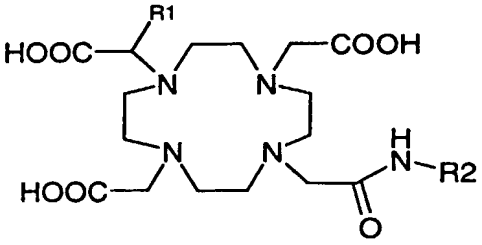
1,4-alpha substitution



1,7-alpha substitution



1,4-alpha substitution DO3A-Amides



1,7-alpha substitution DO3A-Amides

Fig. 3

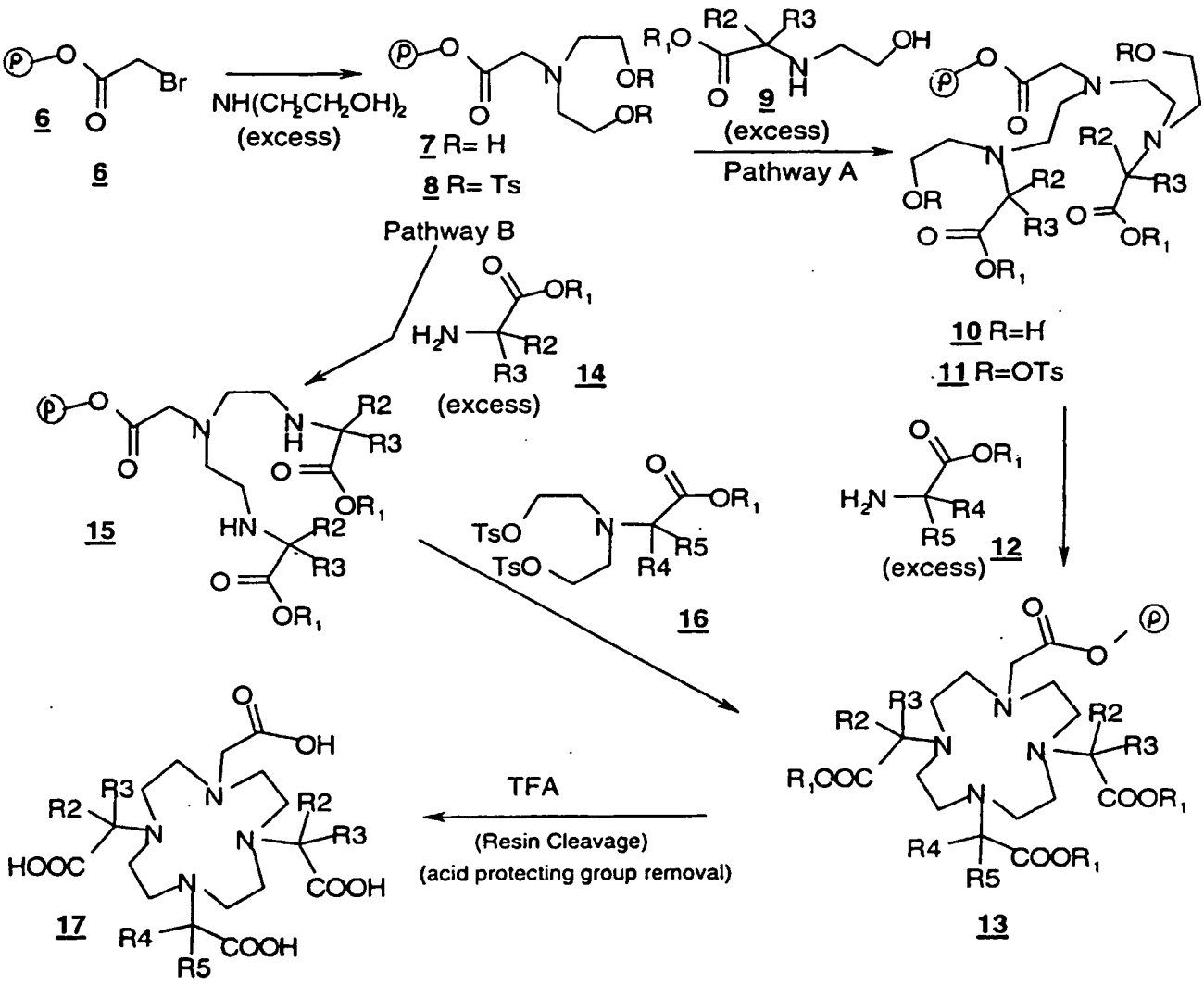

6
NH(CH2CH2OH)2
(excess)
7 R= H
8 R= Ts
9
(excess)
Pathway A
10 R=H
11 R=OTs
Pathway B
14
(excess)
15
16
12
(excess)
13
TFA
(Resin Cleavage)
(acid protecting group removal)
17

Fig. 4

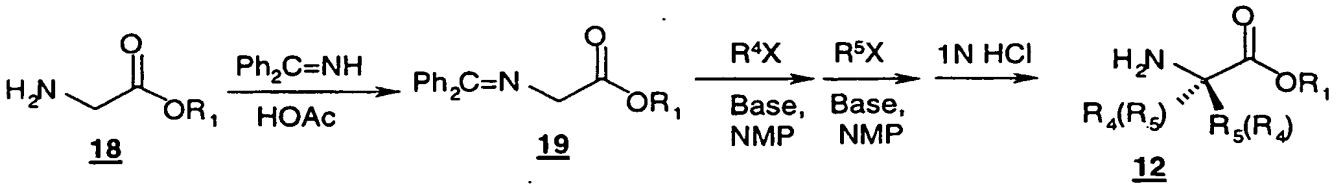

Ph2C=NH
HOAc
R4X
Base, NMP
R5X
Base, NMP
1N HCl
18
19
12

Fig. 5

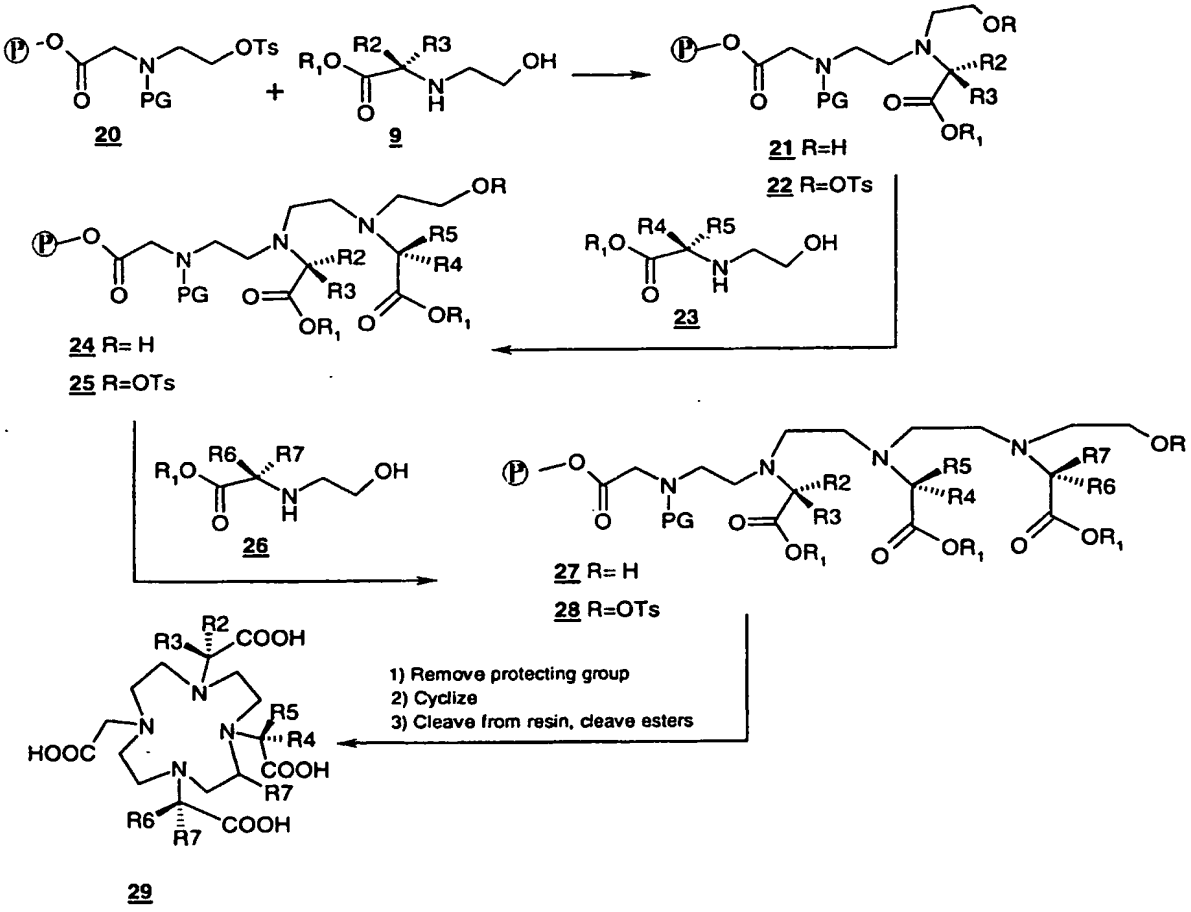
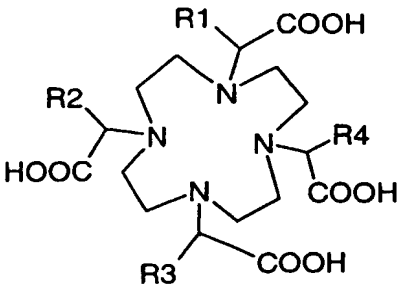
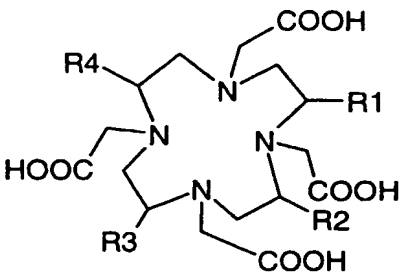

20
9
21 R=H
22 R=OTs
23
24 R= H
25 R=OTs
26
27 R= H
28 R=OTs
1) Remove protecting group
2) Cyclize
3) Cleave from resin, cleave esters
29

Fig. 6



30



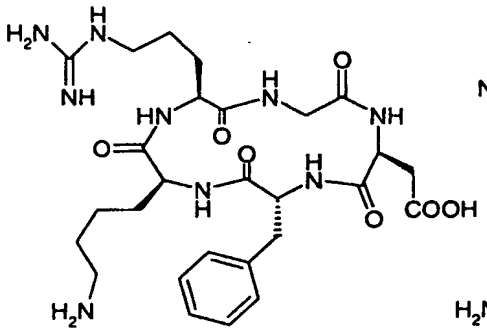
31

R1,R2,R3,R4= Z-M

Z= linker/spacer of varible length, shape, flexibility

M= RDG mimic that selectively antagonizes avb3 intetrin

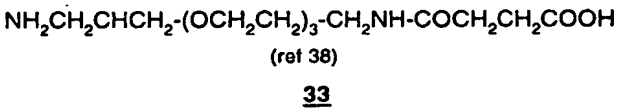
Fig. 7



32

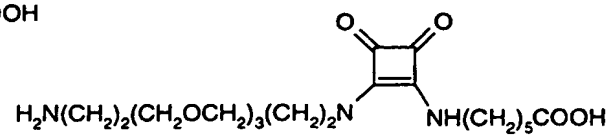
c(RDGfK)

cyclo-(-Arg-Gly-Asp-D-Phe-Lys-)



(ref 38)

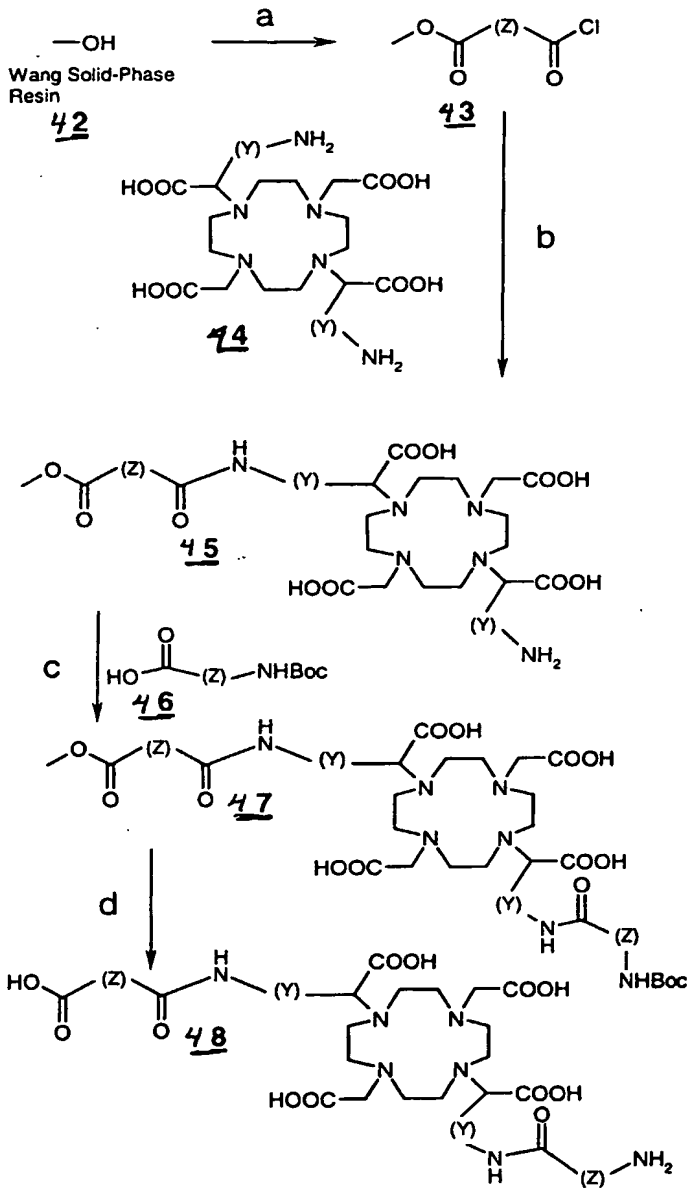
33



(ref 39)

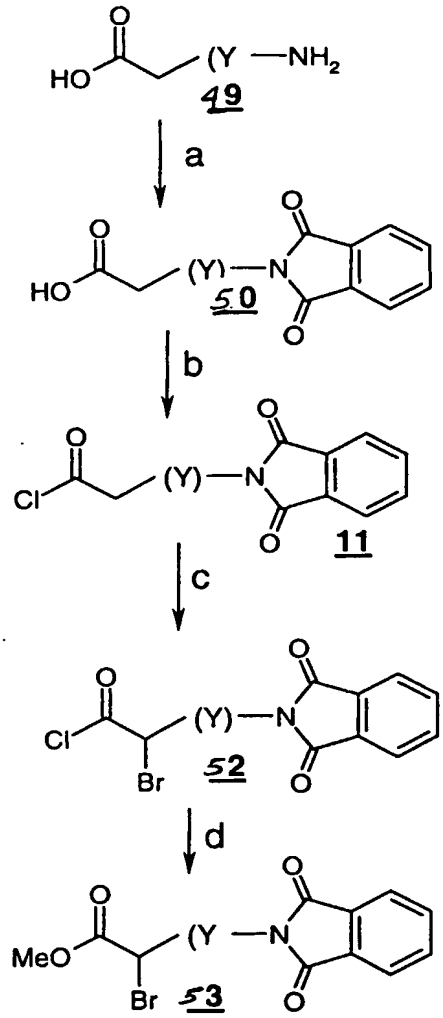
34

Fig. 8



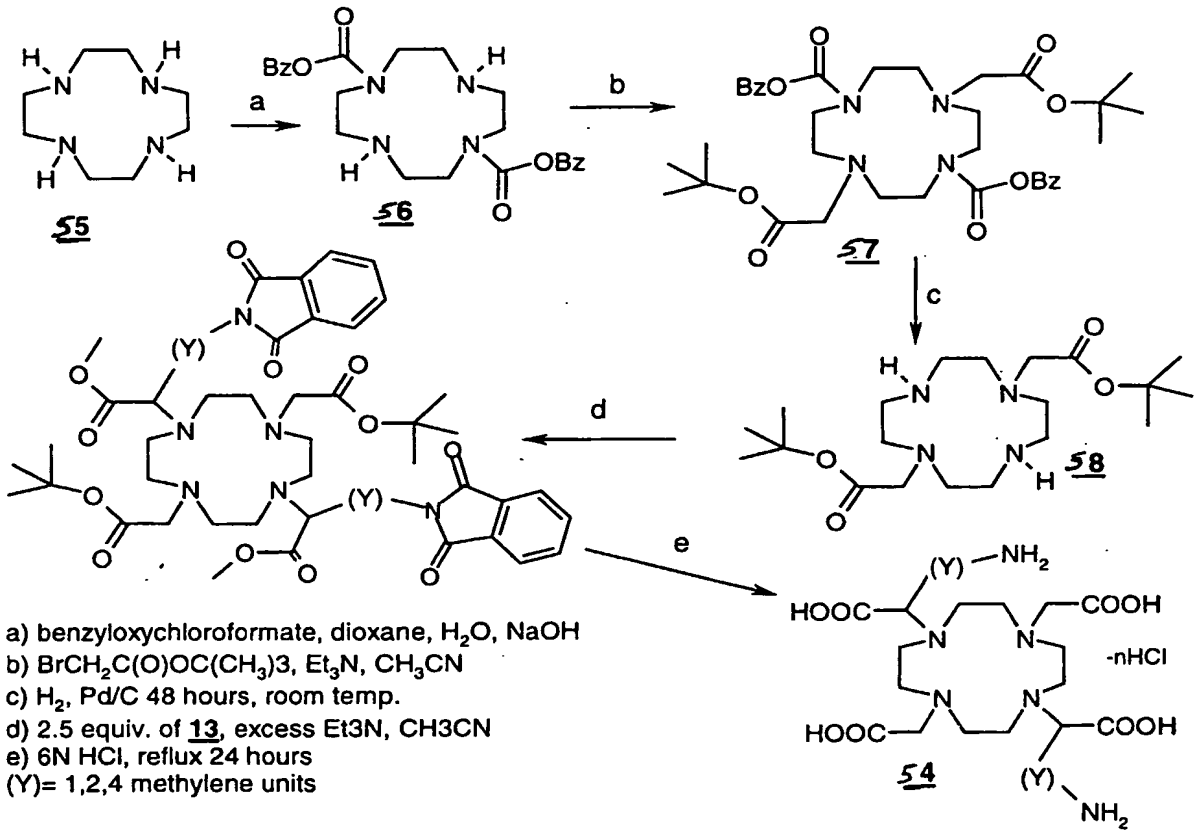
a) symmetrical acid chloride, pyridine, CH_2Cl_2;
b) DMF, Et_3N;
c) carbodiimide coupling or acid chloride;
d) Trifluoroacetic acid/CH_2Cl_2 50/50
(Y)= 1,2,4 methylene units
(Z)= variable spacer groups

Fig. 9



a) phthalic anhydride, toluene, reflux;
b) thionyl chloride, toluene, reflux;
c) N-Bromosuccinimide,CCl4, reflux;
d) quench in MeOH
(Y)= 1,2,4 methylene units

Fig. 10



a) benzyloxychloroformate, dioxane, H_2O, NaOH
b) $BrCH_2C(O)OC(CH_3)3$, Et_3N, CH_3CN
c) H_2, Pd/C 48 hours, room temp.
d) 2.5 equiv. of **13**, excess Et3N, CH3CN
e) 6N HCl, reflux 24 hours
(Y)= 1,2,4 methylene units

Fig. 11

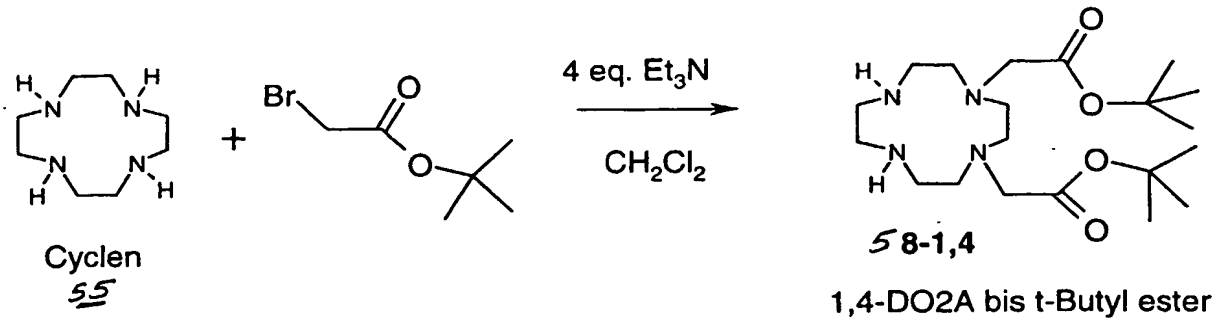

4 eq. Et_3N
CH_2Cl_2
Cyclen
55
58-1,4
1,4-DO2A bis t-Butyl ester

Fig. 12

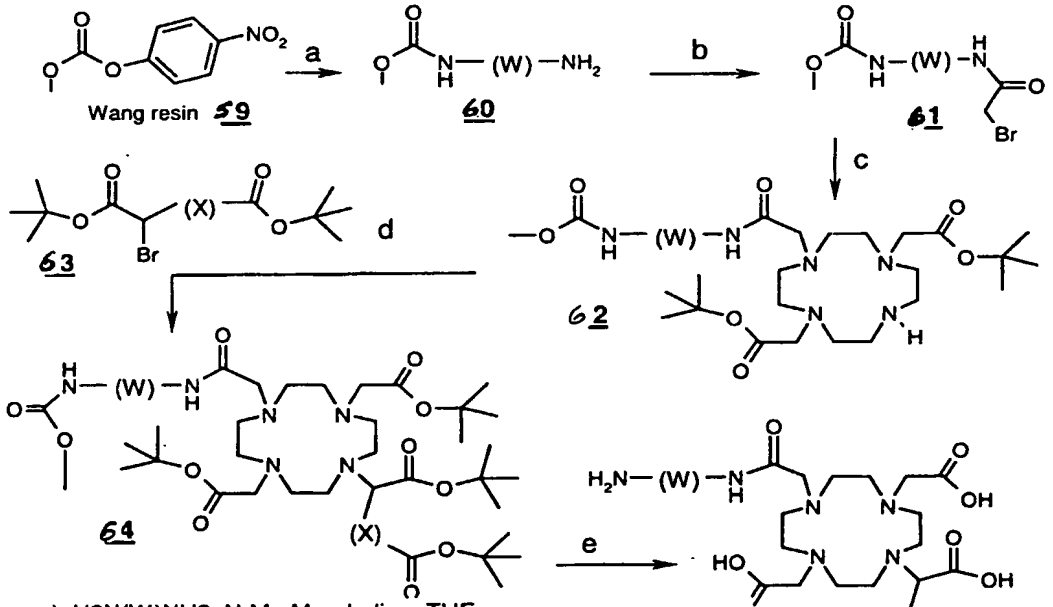
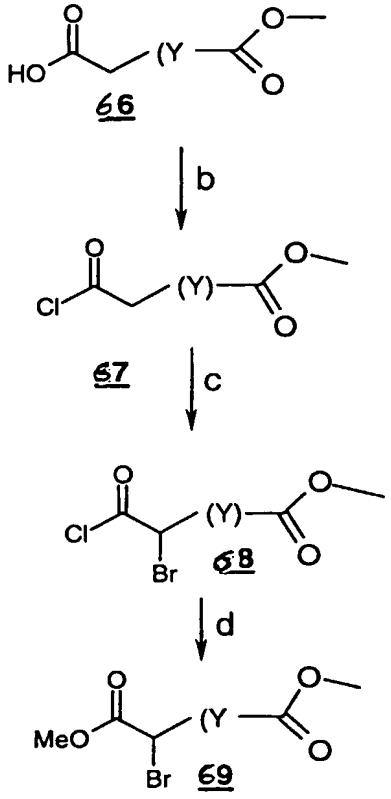
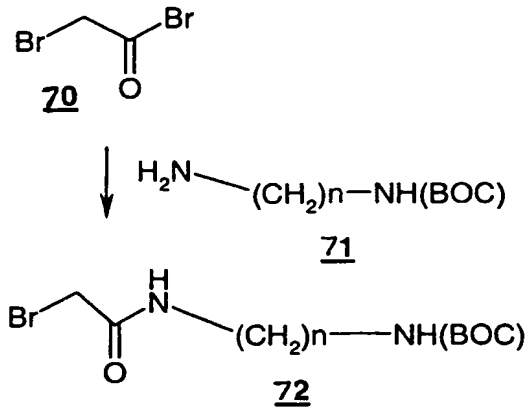

Wang resin 59
60
61
62
63
64
65
a) H2N(W)NH2, N-Me-Morpholine, THF
b) Bromoacetyl bromide, CH_2Cl_2, diisopropyl ethyl amine
c) 18, CH_2Cl_2, diisopropyl ethyl amine
d) CH_2Cl_2, diisopropyl ethyl amine
e) Trifluoroacetic acid, CH2Cl2
(X)= variable spacer unit (-CH2-, -CH2CH2-, and -CH2CH2CH2-)
(W)= variable spacer unit (-(CH2)n where n=2,3,4,5,6,)

Fig. 13



b) thionyl chloride, toluene, reflux;
c) N-Bromosuccinimide,CCl4, reflux;
d) quench in MeOH
(Y)= 0 to 4 methylene units

Fig. 14



n= 2,3,4,5,6

Fig. 15

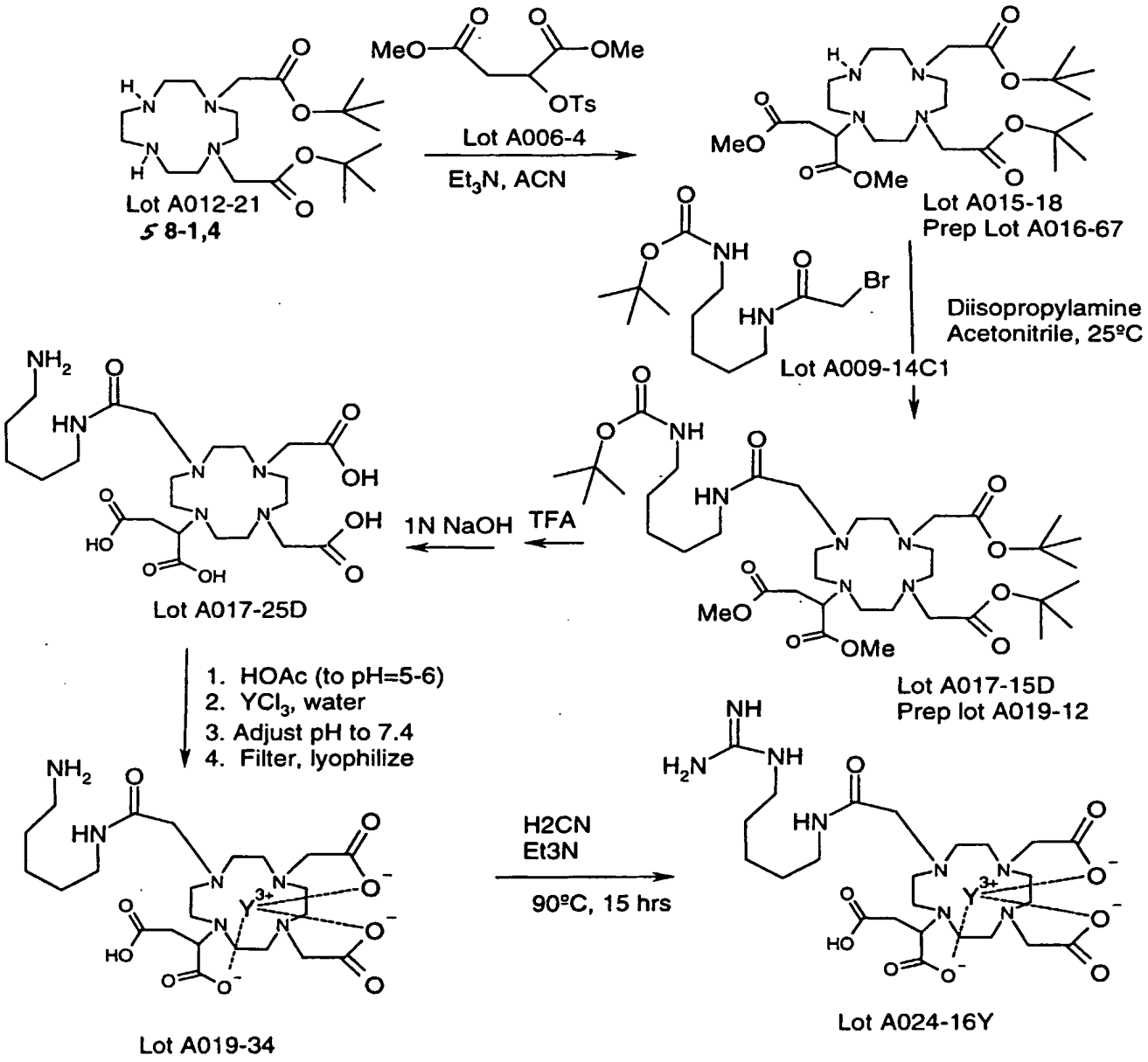
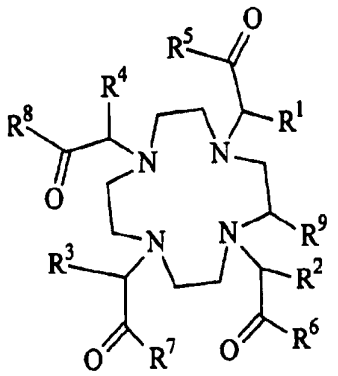

Lot A012-21
5 8-1,4
MeO
OMe
OTs
Lot A006-4
Et3N, ACN
Lot A015-18
Prep Lot A016-67
Diisopropylamine
Acetonitrile, 25ºC
Lot A009-14C1
TFA
1N NaOH
Lot A017-25D
Lot A017-15D
Prep lot A019-12
1. HOAc (to pH=5-6)
2. YCl3, water
3. Adjust pH to 7.4
4. Filter, lyophilize
H2CN
Et3N
90ºC, 15 hrs
Lot A019-34
Lot A024-16Y

Fig. 16

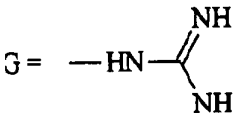


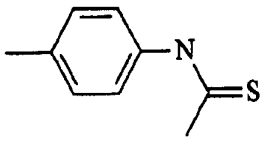
DOTA Based Species

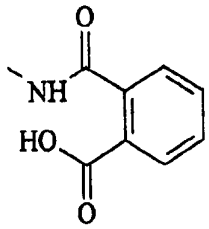
DOTA Based Species	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
A011-65C	CO-B-CH_3	H	H	H	OC_2H_5	OH	$NH(CH_2)_3NH_2$	-OH	H
A013-17	$-(CH_2)_2NH_2$	$-(CH_2)_2NH_2$	H	H	-OH	-OH	OH	-OH	H
A017-79J	$-((CH_2)_2G$	$-(CH_2)_2G$	H	H	-OH	-OH	-OH	-OH	H
A017-80D	$-(CH_2)_2$-G	H	$-(CH_2)_2$-G	H	-OH	-OH	-OH	-OH	H
A017-80K	$-(CH_2)_4$-G	H	$-(CH_2)_4$-G	H	-OH	-OH	-OH	-OH	H
A007-26	H	$-(CH_2)_2$-S	H	H	$-NH(CH_2)_6NH_2$	-OH	OH	-OH	H
A008-43	H	H	H	H	-OH	-OH	OH	-OH	$-CH_2$-A-NH-$(CH_2)_2$-NH_2
A012-17	H	$-(CH_2)_2$-S	H	H	$-NH(CH_2)_5NH_2$	-OH	OH	-OH	H
A012-19	H	$-(CH_2)_2$-S	H	H	$-NH(CH_2)_4NH_2$	-OH	OH	-OH	H
A011-75 (B-E)	H	$-CH_2CO_2H$	H	H	$-NH(CH_2)_nNH_2$ n=3-6	-OH	OH	-OH	H
A017-50 (A-D)	H	$-CH_2CO_2H$	H	H	$-NH(CH_2)_n$-G n = 3-6	-OH	-OH	-OH	H
A017-21 (A-E)	$-(CH_2)_2CO_2H$	H	H	H	-OH	$-NH(CH_2)_nNH_2$ n = 2-6	OH	-OH	H
A017-25 (A-E)	$-CH_2CO_2H$	H	H	H	-OH	$-NH(CH_2)_nNH_2$ n = 2-6	OH	-OH	H
A024-16 (Q-U)	$-(CH_2)_2CO_2H$	H	H	H	-OH	$-NH(CH_2)_n$-G n = 2-6	OH	-OH	H
A024-16(V-Z)	$-CH_2CO_2H$	H	H	H	-OH	$-NH(CH)_n$-G n = 2-6	OH	-OH	H

Fig. 17

DOTA Based Species	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
A011-97 (A-E)	$-(CH_2)_2CO_2H$	H	H	H	-OH	-OH	$NH(CH_2)_nNH_2$ n = 2-6	-OH	H
A011-97 F	$-CH_2CO_2H$	H	H	H	-OH	-OH	$NH(CH_2)_2NH_2$	-OH	H
A013-67(A-E)	$-(CH_2)_3-CO_2H$	H	H	H	-OH	-OH	$-NH(CH_2)_nNH_2$ n = 2-6	-OH	H
A017-79 (E-H)	$-(CH_2)_2CO_2H$	H	H	H	-OH	-OH	$-NH(CH_2)_n$-G n = 2-6	-OH	H
A016-46	$-(CH_2)_3CO_2H$	H	H	H	-OH	-OH	$-NH(CH_2)_2-NH_2$	-OH	H
A024-16 (M-P)	$-(CH_2)_3CO_2H$	H	H	H	-OH	-OH	$-NH(CH_2)_n$-G n=3-6	-OH	H
A013-77	$-(CH_2)_2NH_2$	H	$-(CH_2)_3CO_2H$	H	-OH	-OH	OH	-OH	H
A013-79	$-(CH_2)_4NH_2$	H	$-(CH_2)_3CO_2H$	H	-OH	-OH	OH	-OH	H
A008-59	H	$-(CH_2)_2-NH_2$	H	$-(CH_2)_2-NH_2$	-OH	-OH	OH	-OH	H
A011-35	$(CH_2)_2NH_2$	$(CH_2)_2-NH_2$	H	H	-OH	-OH	-OH	-OH	H
A017-79D	$-(CH_2)_2$-G	H	$-(CH_2)_2$-G	H	-OH	-OH	OH	-OH	H
A013-19	$-(CH_2)_4-NH_2$	H	$-(CH_2)_4-NH_2$	H	-OH	-OH	OH	-OH	H
A017-79 (B-C)	H	H	H	H	-OH	-OH	OH	-OH	$ANH(CH_2)_nG$ n = 2, 4
A008-43	H	H	H	H	-OH	-OH	-OH	-OH	$ANH(CH_2)_2NH_2$
A007-29	H	H	H	H	-OH	-OH	OH	-OH	$ANH(CH_2)_4NH_2$

G = 

A = 

S = 

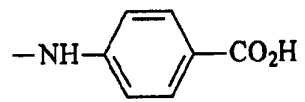
B = 

Fig. 17